chain altered distribution in a much higher proportion of patients with X-linked AS [5].

It is our experience that skin biopsy, examined with conventional, and if needed, with confocal microscopy, is able to virtually detect (almost) all cases of X-linked AS [5], thus allowing to avoid or to postpone more invasive and/or expensive diagnostic procedure like renal biopsy and genetic investigations, which, in addition, are not diagnostic in all cases.

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Reply from the Author

I thank Professors Kashtan and Rizzoni and Dr. Massella for their comments. They rightly point out the value of immunostaining of renal biopsies for the diagnosis of X-linked and autosomal Alport syndrome and the utility of skin immunofluorescence in diagnosis of many cases of X-linked Alport syndrome. The use of confocal laser scanning microscopy (CLSM) [1–3] is an elegant technique to improve the spatial resolution of α5(IV) chain distribution in basement membranes.

Ueda et al [3], also using CLSM, have reported that compared with α2(IV), α5(IV) expression in GBM is reduced in patients with TBMD. The reduction in α5(IV) but not α3(IV) and α4(IV) is difficult to reconcile with the genetic evidence implicating mutations of COL4A3 and COL4A4 in TBMD.

Confirmation and clarification of the results of CLSM of EBM and GBM is eagerly awaited. Until sequencing of the relevant collagen genes or other comprehensive genetic testing is routinely and readily available, immunofluorescence of skin biopsies is a minimally invasive means for diagnosis of many cases of X-linked Alport syndrome. If quantitative comparisons of the different α(IV) chains in GBM permit a positive diagnosis of TBMD, this will further strengthen our diagnostic hand.

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Diagnosis of Alport syndrome

To the Editor: Professor Gregory's recent editorial [1] addresses the difficulties that may arise in attempts to distinguish Alport syndrome and thin basement membrane nephropathy, particularly in children. Positive diagnosis of the X-linked and autosomal-recessive forms of Alport syndrome may be made by immunostaining of renal biopsy specimens for alpha chains of type IV collagen [2, 3]. X-linked Alport syndrome can also be diagnosed by immunostaining of skin biopsy specimens for the alpha5 chain of type IV collagen [4].

There are patients who exhibit expression of type IV collagen chains that is indistinguishable from control, despite the presence of pathogenic mutations in the COL4A3, COL4A4, or COL4A5 gene [3, 4]. In these cases, estimation of prognosis and genetic counseling would be greatly aided by the availability of molecular genetic diagnostic services. More than 80% of mutations in the COL4A5 gene can be identified by direct nucleotide sequencing [5].

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Dialysis dose and gender: A different hypothesis

To the Editor: A recent report [1] suggested that females who are smaller than males need higher dialysis dose (Kt/V) than males. The idea that smaller persons require higher Kt per L of V is not new [2], and suggests that a 0-intercept rule for judging Kt per unit of V is incorrect [3].

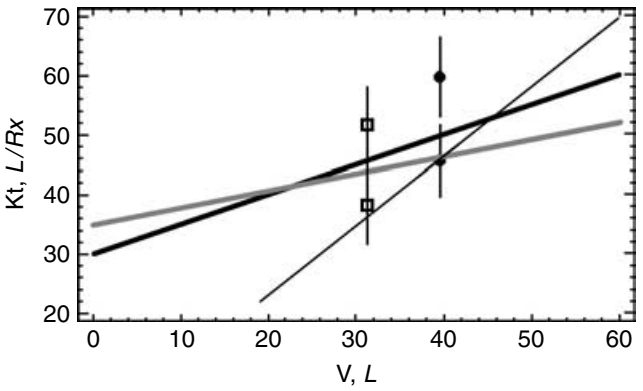

Fig. 1. Illustration of three relationships discriminating the high (upper symbols) and low (lower symbols) Kt/V groups for males (solid circles) and females (open squares) in the HEMO study. The relationships are 1) Kt = 1.16 V (thin black line) representing the low dose HEMO study Kt/V for both genders, 2) Kt = 30 + 0.5 V (thick black line), and 3) 35 + 0.3 V (thick gray line).

Figure 1 illustrates a non-0 intercept rule (thick black line: Kt = 30 + 0.5 V) [3]. The mean Kt ± SD (Table 3) [1] is shown for females (squares) and males (circles) at the mean V (Table 2) [1] for the high (upper symbols) and low (lower symbols) hemodialysis (HEMO) treatment groups. The steep, thin black line is a 0-intercept Kt/V rule (Kt = 0 + 1.16 V) [1]. All groups were treated at or above the Kt for their V by that rule. Females in the low treatment group (Kt = 38.2; eKt/V = 1.17), however, had marginally worse ($P = 0.02$) survival than females in the high treatment group [1].

The gray line (Kt = 35 + 0.3 V) is a rotation of the earlier black line [3], and better discriminates among groups according to outcome. Only low Kt/V females received substantially suboptimal therapy according to this illustrative rule.

The point of this exercise was not to recommend a new rule for judging treatment. It only shows that one need not resort to speculations about different uremic toxin generation in males and females [1] to explain this marginal survival difference. All one needs to do is accept the possibility that a 0-intercept Kt/V rule may be suboptimal.

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